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Invited Editorial Comment

Liability, Thresholds, Malformations, and Syndromes

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The observations by Lurie and Ferencz [1996], that congenital heart malformations in certain Mendelian syndromes have the same proportions as in the general population, draw attention to an important but underappreciated relationship, namely, that factors which influence susceptibility to specific malformations may act by influencing the normal developmental pattern.

The basis for this idea is the multifactorial threshold model, which postulates that many genes and environmental factors interact to determine a continuous distribution of susceptibility (liability), which is separated by a threshold into discontinuous parts, i.e., affected and unaffected [Nora et al., 1994]. In the case of pyloric stenosis, the classical human example, the liability distribution could be the width of the pyloric canal, and the threshold the degree of narrowness at which it becomes obstructed. In the case of cleft palate, extensively studied in the mouse [Fraser, 1980, 1989], the distribution of liability can be thought of as the stage (relative to the embryo as a whole) at which the palatal shelves manage to overcome the resistance of the intervening tongue, and move from the vertical to the horizontal, to meet and fuse. The threshold is the latest stage at which the shelves can come up and still reach each other, and beyond which a cleft palate will result. Anything that disturbs synchrony by delaying shelf closure (such as maternal cortisone) will increase the frequency of cleft palate. The closer an embryo is to the threshold, the more likely it is that a delay will push it beyond the threshold, i.e., the more susceptible it is to cleft palate (Fig. 1).

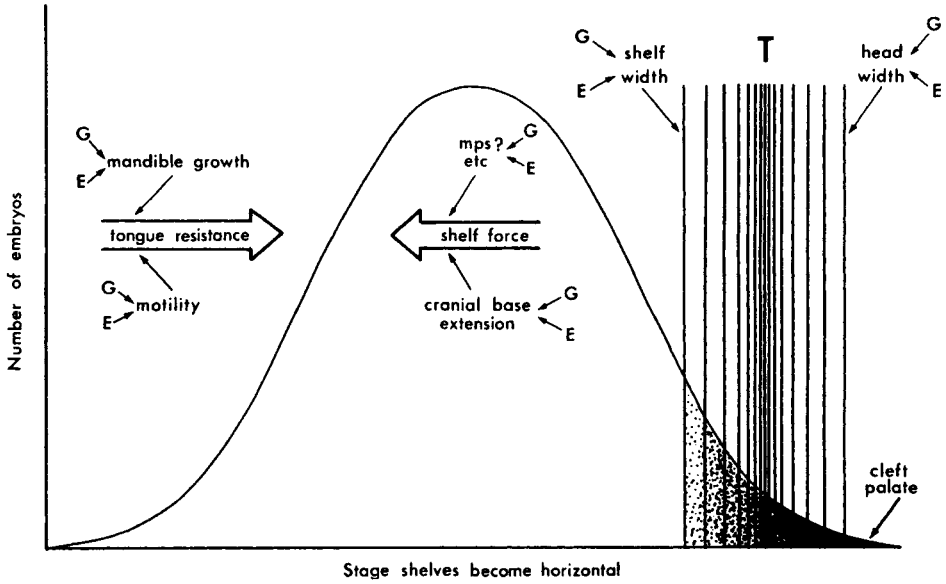

Fig. 1. Multifactorial threshold model for cortisone-induced cleft palate.

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Various components have been identified that make the embryo more susceptible to the delaying agent, either by moving the distribution to the right (increased tongue resistance, decreased shelf force), or the threshold to the left (decreased shelf width, increased head width). Each of these components can be influenced by genes and environmental factors. The important thing is that *the embryo's susceptibility is influenced by its normal developmental pattern,* in this case, the stage at which the shelves normally come up. The later the *normal* closure is, the higher the frequency of induced cleft palate.

It also follows from the model (though this has not been so well-documented) that the frequency of cleft palate would be increased by increasing the *variance* of the distribution, by any sort of influence that increases developmental instability. Increasing the variance increases the proportion of embryos that falls beyond the threshold, even without changing the position of the distribution or threshold [Fraser, 1994]. Again, the closer the distribution is to the threshold, the more clefts will be induced by a delaying agent.

There are other examples. Maternal treatment with aspirin causes medial cleft lip in the C57BL strain of mouse, and lateral cleft lip in the A/Jax strain, the difference being related to a difference in embryonic face shape [Trasler, 1968]. Maternal treatment with dextroamphetamine causes ventricular septal defect in the C57BL strain, and atrial septal defect in the A/Jax strain, in which the atrial septum closes later [Nora et al., 1968; Fraser and Rosen, 1975].

The message of Lurie and Ferencz [1996] is: each embryo has specific constellations of genes that determine its liability to specific malformations; a major insult, such as the 3C mutant gene (or, for that matter, an environmental teratogen) may destabilize several developmental systems, either by creating dyssynchrony or increasing variance; the type of malformation produced will depend on how the embryo's genes influence its particular set of normal developmental patterns and hence its susceptibilities. And that may be why the same mutant gene causes different malformations in different embryos.

The hypothesis is testable, though the answers may require large bodies of data, since the postulated differences may not be large. For example, do the (unexposed) near relatives of children with phenytoin-induced cleft lip have an increased frequency of cleft lip? Likewise for valproate-induced neural tube defects? Is the frequency of cleft lip higher in sibs when Meckel syndrome patients have cleft lip than when they do not? Similarly the frequency of heart malformations increased in the sibs of patients with any syndrome in which heart malformations sometimes, but not always, occur. And so on.

Perhaps someone has already looked for such differences. If so, let's hear from you!

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